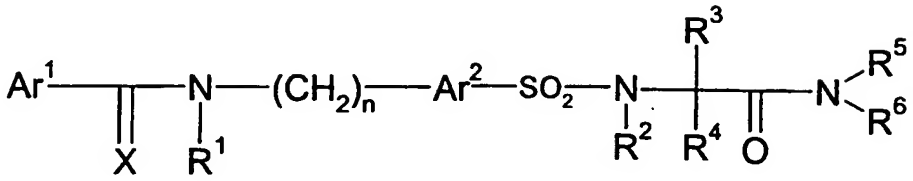
Claims

1. Sulfonyl amino acid derivatives according to formula I



I

with its geometrical isomers, in an optically active form as enantiomers, diastereomers, as well as in the form of racemates, as well as pharmaceutically acceptable salts thereof, wherein

Ar^1 and Ar^2 are independently from each other substituted or unsubstituted aryl or heteroaryl;

X is O or S;

R^1 is hydrogen or an unsubstituted or substituted C_1-C_6-alkyl group, or R^1 could form a substituted or unsubstituted 5-6—membered saturated or unsaturated fused ring with Ar^1, or R^2 and R^4 form a substituted or unsubstituted 5-6—membered saturated or non-saturated ring;

R^2 is hydrogen or a substituted or unsubstituted C_1-C_6-alkyl group;

n is an integer from 0 to 5;

R^3 and R^4 are independently from each other selected from the group comprising or consisting of natural amino acid residues or synthetic amino acid residues, hydrogen, substituted or unsubstituted C_1-C_6-alkyl, substituted or unsubstituted C_1-C_6-alkoxy, NH_2, SH, thioalkyl, acylamino, aminocarbonyl, substituted or unsubstituted C_1-C_6-alkoxycarbonyl, aryl, heteroaryl, substituted or unsubstituted 4-8-membered cyclic alkyl, optionally containing 1-3 heteroatoms, carboxyl, cyano, halogen, hydroxy, nitro, acyloxy, acylamino, sulfoxy, sulfonyl, C_1-C_6-thioalkoxy, whereby at least one of R^3 and/or R^4 must be an amino acid residue;

R^5 is H or substituted or unsubstituted C_1-C_6-alkyl;

R^6 is selected from the group comprising or consisting of H, substituted or unsubstituted C_1-C_6-aliphatic alkyl, substituted or unsubstituted saturated cyclic C_4-C_8-alkyl optionally containing 1-3 heteroatoms and optionally fused with an aryl or an heteroaryl; or R^6 is a substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl,

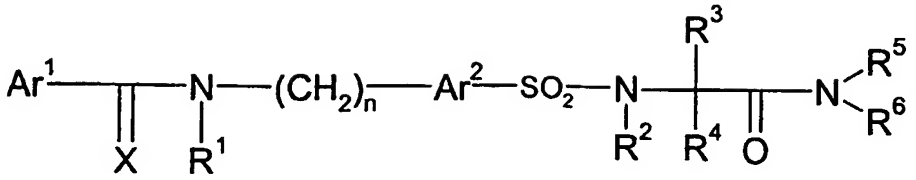
whereby said aryl or heteroaryl groups are optionally substituted with substituted or unsubstituted C_1-C_6-alkyl, like trihalomethyl, substituted or unsubstituted C_1-C_6-alkoxy, substituted or unsubstituted C_2-C_6-alkenyl, substituted or unsubstituted C_2-C_6-alkynyl, amino, acylamino, aminocarbonyl, substituted or unsubstituted C_1-C_6-alkoxycarbonyl, aryl, carboxyl, cyano, halogen, hydroxy, nitro, acyloxy, acylamino, sulfoxy, sulfonyl, C_1-C_6-thioalkoxy; or

R^5 and R^6 taken together could form a substituted or unsubstituted 4-8-membered saturated cyclic alkyl or heteroalkyl group;

with the proviso that if Ar^1 is a 4-chlorophenyl, while Ar^2 is thienyl, X = O, n = 1, the residues R^1, R^2, R^3, R^5 and R^6 are H, R^4 shall not be methyl or (4-hydroxy-phenyl)ethyl, and R^2 shall not be propyl while R^1, R^3, R^5 are H, R^4 is methyl and R^6 is 2-methylphenyl;

with the further proviso that if Ar^1 is a 4-chlorophenyl or a 2,4-bischlorophenyl residue, while Ar^2 is phenyl, X = O, n = 1, the residues R^1, R^2, R^3 and R^5 are all H and R^6 is CH_2-CO_2CH_3; R^4 shall not be selected form the group consisting of H, CH_3, CH_2-C_6H_4-OH-4, CH_2-CH-$(CH_3)_2$.

2. Sulfonyl amino acid derivatives according to formula I



I

with its geometrical isomers, in an optically active form as enantiomers, diastereomers, as well as in the form of racemates, as well as pharmaceutically acceptable salts thereof, wherein

Ar^1 and Ar^2 are independently from each other substituted or unsubstituted aryl or heteroaryl;

X is O or S;

R^1 is hydrogen or an unsubstituted or substituted C_1-C_6-alkyl group, or R^1 could form a substituted or unsubstituted 5-6—membered saturated or unsaturated fused ring with Ar^1, or R^2 and R^4 form a substituted or unsubstituted 5-6—membered saturated or non-saturated ring;

R^2 is hydrogen or a substituted or unsubstituted C_1-C_6-alkyl group;

n is an integer from 0 to 5;

R^3 and R^4 are independently from each other selected from the group comprising or consisting of natural amino acid residues or synthetic amino acid residues, hydrogen, substituted or unsubstituted C_1-C_6-alkyl, like trihalomethyl, substituted or unsubstituted C_1-C_6-alkoxy, NH_2, SH, thioalkyl, acylamino, aminocarbonyl, substituted or unsubstituted C_1-C_6-alkoxycarbonyl, aryl, heteroaryl, substituted or unsubstituted 4-8-membered cyclic alkyl, optionally containing 1-3 heteroatoms, carboxyl, cyano, halogen, hydroxy, nitro, acyloxy, acylamino, sulfoxy, sulfonyl, C_1-C_6-thioalkoxy, whereby at least one of R^3 and/or R^4 must be an amino acid residue;

R^5 is H or substituted or unsubstituted C_1-C_6-alkyl;

R^6 is selected from the group comprising or consisting of H, substituted or unsubstituted C_1-C_6-aliphatic alkyl, substituted or unsubstituted saturated cyclic C_4-C_8-

alkyl optionally containing 1-3 heteroatoms and optionally fused with an aryl or an heteroaryl; or R^6 is a substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, whereby said aryl or heteroaryl groups are optionally substituted with substituted or unsubstituted C_1-C_6-alkyl, like trihalomethyl, substituted or unsubstituted C_1-C_6-alkoxy, substituted or unsubstituted C_2-C_6-alkenyl, substituted or unsubstituted C_2-C_6-alkynyl, amino, acylamino, aminocarbonyl, substituted or unsubstituted C_1-C_6-alkoxycarbonyl, aryl, carboxyl, cyano, halogen, hydroxy, nitro, acyloxy, acylamino, sulfoxy, sulfonyl, C_1-C_6-thioalkoxy; or

R^5 and R^6 taken together could form a substituted or unsubstituted 4-8-membered saturated cyclic alkyl or heteroalkyl group;
for use as a medicament.

3. A sulfonyl amino acid derivatives according to claim 1 or 2, wherein n is 1.

4. A sulfonyl amino acid derivative according to any of the preceding claims, wherein Ar^1 and Ar^2 are independently selected from the group comprising or consisting of phenyl, thienyl, furyl, pyridyl, said residues being optionally substituted by at least one sub-stituted or unsubstituted C_1-C_6-alkyl, like trihalomethyl, substituted or unsubstituted C_1-C_6-alkoxy, substituted or unsubstituted C_2-C_6-alkenyl, substituted or unsubstitu-ted C_2-C_6-alkynyl, amino, acylamino, aminocarbonyl, substituted or unsubstituted C_1-C_6-alkoxycarbonyl, aryl, carboxyl, cyano, halogen, hydroxy, nitro, acyloxy, acylamino, sulfoxy, sulfonyl, substituted or unsubstituted C_1-C_6-thioalkoxy.

Sub A1

5. A sulfonyl amino acid derivative according to any of the preceding claims, wherein at least one of R^3 and/or R^4 is selected from the group consisting of the following natural amino acid residues : alanyl, arginyl, asparaginyl, aspartyl, cysteinyl, glutaminyl, glutamyl, glycyl, histidyl, isoleucyl, leucyl, lysyl, methionyl, phenylalanyl, prolyl, seryl, threonyl, tryptophanyl, tyrosyl, valyl.

6. A sulfonyl amino acid derivative according to any of the preceding claims, wherein

Ar^1 is an unsubstituted or substituted phenyl, preferably 4-chlorophenyl, X is O, R^1, R^2, R^3 and R^4 are hydrogen, n is 1, Ar^2 is thienyl, R^5 is H or C_1-C_6-alkyl;

R^6 is selected from the group comprising or consisting of H, a substituted or unsubstituted C_1-C_6-aliphatic alkyl - e.g. a C_1-C_6-alkylamino aryl, a C_1-C_6-alkylamino heteroaryl, a substituted or unsubstituted cyclic C_4-C_8-alkyl containing optionally 1-3 heteroatoms and being optionally fused with an unsubstituted or substituted aryl or heteroaryl; or R^6 is an unsubstituted or substituted aryl or heteroaryl;

said aryl or heteroaryl groups are optionally substituted by substituted or unsubstituted C_1-C_6-alkyl, like trihalomethyl, substituted or unsubstituted C_1-C_6-alkoxy, substituted or unsubstituted C_2-C_6-alkenyl, substituted or unsubstituted C_2-C_6-alkynyl, amino, acylamino, aminocarbonyl, substituted or unsubstituted C_1-C_6-alkoxycarbonyl, aryl, carboxyl, cyano, halogen, hydroxy, nitro, sulfoxy, C_1-C_6- thio alkoxy; or

R^5 and R^6 taken together could form an unsubstituted or substituted 4-8-membered saturated cyclic alkyl or heteroalkyl group, e.g. an unsubstituted or substituted piperidino group.

7. A sulfonyl amino acid derivative according to any of the preceding claims, wherein

R^5 is H; and R^6 is a C_1-C_6-alkyl which is substituted by an aryl, an heteroaryl group or an aminoaryl, aminoheteroaryl, aryloxy, heteroaryloxy, whereby said aryl and heteroaryl groups are optionally substituted by substituted or unsubstituted C_1-C_6-alkyl, like trihalomethyl, substituted or unsubstituted C_1-C_6-alkoxy, substituted or unsubstituted C_2-C_6-alkenyl, substituted or unsubstituted C_2-C_6-alkynyl, amino, acylamino, aminocarbonyl, substituted or unsubstituted C_1-C_6-alkoxycarbonyl, substituted or unsubstituted aryl, carboxyl, cyano, halogen, hydroxy, nitro, sulfoxy, C_1-C_6-thioalkoxy.

8. Sulfonyl amino acid derivatives according to claim 7, wherein R^6 is a substituted or unsubstituted pyridyl group.

9. A sulfonyl amino acid derivative according to any of the preceding claims which is selected from the following group :

4-chloro-N-({5-[({2-[(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]amino}ethyl)-amino]-2-oxoethyl}amino)sulfonyl]thien-2-yl}methyl)benzamide

4-chloro-N-[(5-{[(2-{[2-({5-nitropyridin-2-yl}amino)ethyl]amino}-2-oxoethyl)-amino]sulfonyl}thien-2-yl)methyl]benzamide

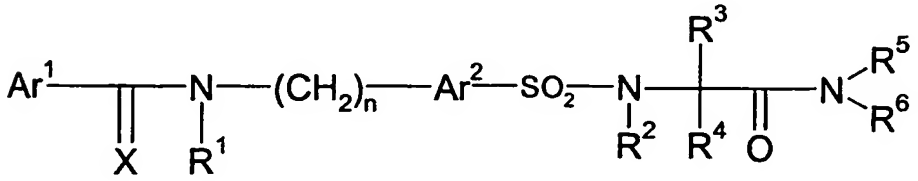
4-chloro-N-({5-[({2-oxo-2-[(2-{[3-(trifluoromethyl)pyridin-2-yl]amino}ethyl)-amino]ethyl}amino)sulfonyl]thien-2-yl}methyl)benzamide

4-chloro-N-({5-[({2-oxo-2-[(2-{[5-(trifluoromethyl)pyridin-2-yl]amino}ethyl)-amino]ethyl}amino)sulfonyl]thien-2-yl}methyl)benzamide

N-({5-[({2-[4-(1H-1,2,3-benzotriazol-1-yl)piperidin-1-yl]-2-oxoethyl}amino)-sulfonyl]thien-2-yl}methyl)-4-chlorobenzamide

4-chloro-N-[(5-{[(2-oxo-2-{3-[(trifluoromethyl)sulfonyl]anilino}ethyl)amino]-sulfonyl}thien-2-yl)methyl]benzamide

10. Use of a sulfonyl amino acid derivative according to formula I



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wherein Ar^1 and Ar^2 are independently from each other substituted or unsubstituted aryl or heteroaryl;

X is O or S;

R^1 is hydrogen or an unsubstituted or substituted C_1-C_6-alkyl group, or R^1 could form a substituted or unsubstituted 5-6—membered saturated or unsaturated fused

ring with Ar^1, or R^2 and R^4 form a substituted or unsubstituted 5-6—membered saturated or non-saturated ring;

R^2 is hydrogen or a substituted or unsubstituted C_1-C_6-alkyl group;

n is an integer from 0 to 5;

R^3 and R^4 are independently from each other selected from the group comprising or consisting of natural amino acid residues or synthetic amino acid residues, hydrogen, substituted or unsubstituted C_1-C_6-alkyl, like trihalomethyl, substituted or unsubstituted C_1-C_6-alkoxy, NH_2, SH, thioalkyl, acylamino, aminocarbonyl, substituted or unsubstituted C_1-C_6-alkoxycarbonyl, aryl, heteroaryl, substituted or unsubstituted 4-8-membered cyclic alkyl, optionally containing 1-3 heteroatoms, carboxyl, cyano, halogen, hydroxy, nitro, acyloxy, acylamino, sulfoxy, sulfonyl, C_1-C_6-thioalkoxy, whereby at least one of R^3 and/or R^4 must be an amino acid residue;

R^5 is H or substituted or unsubstituted C_1-C_6-alkyl;

R^6 is selected from the group comprising or consisting of H, substituted or unsubstituted C_1-C_6-aliphatic alkyl, substituted or unsubstituted saturated cyclic C_4-C_8-alkyl optionally containing 1-3 heteroatoms and optionally fused with an aryl or an heteroaryl; or R^6 is a substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, whereby said aryl or heteroaryl groups are optionally substituted with substituted or unsubstituted C_1-C_6-alkyl, like trihalomethyl, substituted or unsubstituted C_1-C_6-alkoxy, substituted or unsubstituted C_2-C_6-alkenyl, substituted or unsubstituted C_2-C_6-alkynyl, amino, acylamino, aminocarbonyl, substituted or unsubstituted C_1-C_6-alkoxycarbonyl, aryl, carboxyl, cyano, halogen, hydroxy, nitro, acyloxy, acylamino, sulfoxy, sulfonyl, C_1-C_6-thioalkoxy; or

R^5 and R^6 taken together could form a substituted or unsubstituted 4-8-membered saturated cyclic alkyl or heteroalkyl group;

for the preparation of a pharmaceutical composition for the modulation of the JNK pathways.

11. Use according to claim 10 for the treatment or prevention of disorders associated with abnormal expression or activity of JNK.

12. Use according to claim 10 or 11 for the treatment or prevention of disorders associated with abnormal expression or activity of JNK2 and/or 3.

13. Use of a sulfonyl amino acid derivative according to formula I in particular according to any of claims 10 to 12 for the treatment of neuronal disorders including epilepsy; Alzheimer's disease, Huntington's disease, Parkinson's disease; retinal diseases, spinal cord injury, head trauma.

14. Use of a sulfonyl amino acid derivative according to formula I in particular according to any of claims 10 to 12 for the treatment of autoimmune diseases including Multiple Sclerosis, inflammatory bowel disease (IBD), rheumatoid arthritis, asthma, septic shock, transplant rejection.

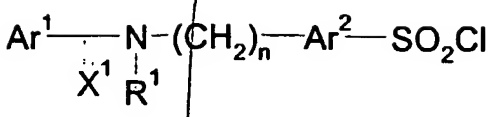
15. Use of a sulfonyl amino acid derivative according to formula I in particular according to any of claims 10 to 12 for the treatment of cancer including breast-, colorectal-, pancreatic cancer.

16. Use of a sulfonyl amino acid derivative according to formula I in particular according to any of claims 10 to 12 for the treatment of cardiovascular diseases including stroke, arteriosclerosis, myocordial infarction, myocordial reperfusion injury.

17. A pharmaceutical composition containing at least one sulfonyl amino acid derivative according to any of the claims 1 to 9 and a pharmaceutically acceptable carrier, diluent or excipient thereof.

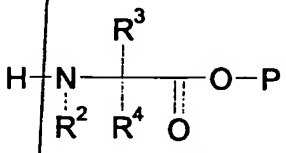
18. Process for the preparation of a sulfonyl amino acid derivative according to any of the claims 1 to 9 comprising or consisting of the steps of :

a) preparing a sulfonyl compound V,



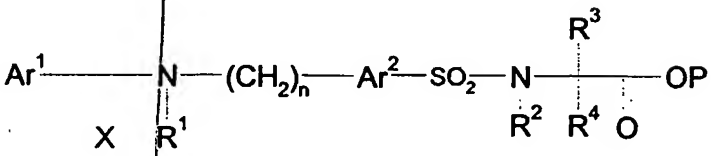
V

b) reacting it with the protected amino acid compound VIII



VIII

thus leading to a compound



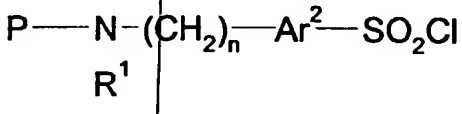
IX

c) said compound IX is subjected to a deprotection and finally

d) a coupling.

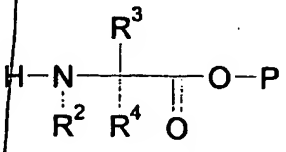
19. Process for the preparation of the sulfonyl amino acid derivatives according to any of the claims 1 to 9 comprising or consisting of the steps of :

a) preparing a protected sulfonyl compound VII



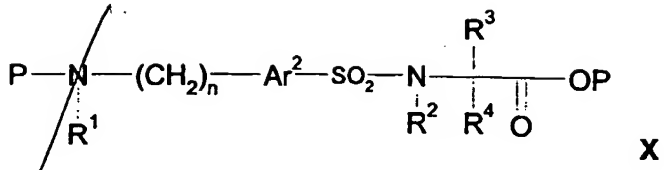
VII

b) reacting it with the protected amino acid compound VIII



VIII

thus leading to a compound



X

e) followed by deprotection;

f) coupling;

g) deprotection, and

h) acylation.